REMARKS/ARGUMENTS

Upon entry of this amendment, claims 40, 54, 61-65, 72-75, 82-86, 93, and 94 will be pending in this application. Claims 95-101 are canceled herein without prejudice to prosecution of the subject matter presented therein at a later date. Claims 40, 54, 61-65, 72-75, 82-86, 93, and 94 are amended herein to overcome rejections raised under 35 U.S.C. § 112, second paragraph. No new matter has been introduced by way of the amendments.

Applicants note with appreciation the reference to rejections rendered moot or withdrawn by the prior response in paragraphs 11-16 of the Office Action.

Formal drawings were filed with the Drawing Review Branch on April 1, 2003. Nonetheless, in an effort to advance prosecution of the application, Applicants submit herewith new formal Figures 1A, 1B, 1C, 2, 3, 4A, 4B, 4C, 4D, 4E, 4F, 5A, 5B, and 5C in accordance with 37 CFR § 1.121. No changes to the drawings have been made. Accordingly, no new matter has been introduced by way of this amendment.

The specification has been amended on page 1 to correct the claim of priority as suggested by the Examiner. The specification also has been amended at pages 39-40 to identify the proprietary nature of the trademarks used therein. Additionally, the specification has been amended at page 61 to update the address for the American Type Culture Collection. No new matter has been introduced by way of these amendments.

I. Provisional Double Patenting Rejection

Claims 40, 54, 63-65, 74, 75, and 84-85 are provisionally rejected for alleged obviousness-type double patenting over claims 38, 44, 45, and 46 of copending application U.S.S.N. 09/921,157. Applicants disagree with the rejection. Nonetheless, without conceding the obviousness of claims 40, 54, 63-65, 74, 75, and 84-85 in view of the cited claims of the copending application, Applicants submit that a terminal disclaimer over Application Serial No. 09/921,157 will be filed upon receipt of an indication of allowability of the cited claims in that case and of claims 40, 54, 63-65, 74, 75, and 84-85 in the present case.

II. The claims as amended overcome the rejections under 35 U.S.C. § 112, second paragraph.

Claims 40, 54, 63-65, 74, 75, and 84-86 are rejected for alleged indefiniteness under 35 U.S.C. § 112, second paragraph.

Claims 40, 54, 74, and 75 are amended herein to recite "amino acid sequence of" SEQ ID NO:3. Similarly, claims 63-65 and 84-86 are amended to recite "nucleotide sequence of" SEQ ID NO:2. Applicants submit that the claim amendments overcome the rejection for alleged lack of clarity under 35 U.S.C. § 112, second paragraph. Applicants respectfully request withdrawal of the rejection.

Claims 40, 74, and 84 are rejected for alleged indefiniteness in recitation of the phrase "exhibits substantially no toxicity, or a substantially reduced toxicity." The term "substantially" often is used in conjunction with another term to describe a particular characteristic of a claimed invention. MPEP §2173.05 (b). Definiteness will be found for use of the term "substantially" where there are general guidelines in the specification (*In re Mattison*, 509 F.2d 563, 184 U.S.P.Q. 484 (C.C.P.A. 1975)) or where one of ordinary skill in the art would understand the meaning of the term (*Andrew Corp. v. Gabriel Electronics*, 847 F.2d 819, 6 U.S.P.Q. 2d 2010 (Fed. Cir. 1988)). Both of these instances occurs in the present case. As previously asserted, one of ordinary skill in the art would understand the use of the term "substantially" in the aforementioned phrase to mean that the polypeptide or fragment being described does not exhibit statistically significant cytotoxic effects. Indeed, Applicants have provided a Declaration of Dr. Del Giudice to substantiate this assertion.

Moreover, the specification provides very clear guidance as to the meaning of the term "substantially" as used in the specification. For example, at page 16, lines 19-29, the terms "purified" and "isolated" are defined as "substantial absence of other biological macromolecules of the same type" – *i.e.*, "at least 75% by weight, more preferably at least 85% by weight, more preferably still at least 95% by weight, and most preferably at least 98% by weight, of biological macromolecules of the same type." In other words, substantially pure means at least 75% pure. Similarly, "substantially no toxicity or a substantially reduced toxicity" means at least a 75% reduction in toxicity.

The Examiner additionally asserts that it is unclear to what kind of toxicity the phrase refers. Applicants disagree. Applicants use the terms "toxin" and "cytotoxin" and

derivatives thereof interchangeably in the specification. Indeed, "cytotoxin" and "toxin" are defined synonymously in the specification at page 5, line 31 to page 6, line 11. The 140 kDa protein set forth in Fig. 2 is the precursor protein to the 100 kDa polypeptide having cytotoxic activity – *i.e.*, vacuolating activity (Specification at page 5, lines 35-39 and page 46, lines 7-29, for example).

In view of the guidance provided by the specification and the knowledge of one of ordinary skill in the art, Applicants maintain that the phrase "substantially no toxicity, or a substantially reduced toxicity" satisfies the requirements of section 112. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim 95 is rejected as being allegedly indefinite for recitation of the term "formulation." That claim has been canceled herein without prejudice. Applicants respectfully request withdrawal of the rejection.

Claims 95 and 99 are rejected under the second paragraph of section 112 for alleged internal inconsistency. Applicants disagree with the rejection. Nonetheless, in an effort to advance prosecution of the application, Applicants have canceled claims 95 and 99 and, accordingly, respectfully request reconsideration and withdrawal of the rejection.

Claims 61, 62, 72, 73, 82, 83, 93, and 94 are rejected for lack of clarity. Those claims have been amended to recite the characteristic "molecular weight." Applicants submit that the amendments to claims 61, 62, 72, 73, 82, 83, 93, and 94 overcome the rejection for alleged lack of clarity under 35 U.S.C. § 112, second paragraph. Applicants respectfully request withdrawal of the rejection.

III. Claims 40, 54, 61-65, 72-75, 82-86, 93, and 94 satisfy the patentability requirements of 35 U.S.C. § 112, first paragraph.

Claims 40, 54, 61-65, 72-75, 82-86, 93, and 94 are rejected under 35 U.S.C. § 112, first paragraph for allegedly containing new matter. Applicants disagree with the rejection. The phrase constituting alleged new matter is "immunologically identifiable by antibodies which react specifically with the polypeptide having the amino acid sequence of SEQ ID NO:3." Support for this language is found throughout the specification as filed. The specification states, for example, that "[t]he *H. pylori* proteins [of the invention] may be used

for producing antibodies, either monoclonal or polyclonal, *specific to* the proteins." Specification at page 15, lines 18-20. Additionally, the specification discloses the preparation of antisera against the *Helicobacter pylori* cytotoxin and the use of the antisera to specifically detect polypeptides immunologically identifiable with the *H. pylori* cytotoxin. *See, e.g.,* Specification at page 45, line 26 to page 46, line 6. As the rejected phrase is fully supported by the application as filed, Applicants respectfully request withdrawal of the rejection.

Claims 40, 54, 61-65, 72-75, 82-85, 93, and 94 are rejected further for alleged lack of written description. Applicants traverse the rejection.

The claims recite a recombinant polypeptide having at least a portion of the amino acid sequence of SEQ ID NO:3, or encoded by at least a fragment of the nucleotide sequence of SEQ ID NO:2, having the properties of being immunologically identifiable by antibodies that react specifically with the polypeptide of SEQ ID NO:3, or with the polypeptide encoded by SEQ ID NO:2, and exhibiting substantially no toxicity or substantially reduced toxicity.

The skilled artisan can envision the claimed polypeptide structure in accordance with the specification and would understand that the inventors were in possession of the claimed invention at the time of filing. Sufficient information has been conveyed in the present specification such that those of skill in the art would recognize the description of the polypeptides as claimed. In particular, the specification discloses functional information – *i.e.*, the characteristics of being immunologically identifiable by antibodies that react specifically with the polypeptide of SEQ ID NO:3, or with the polypeptide encoded by SEQ ID NO:2, and exhibiting substantially no toxicity or substantially reduced toxicity -- as well as structural information – *i.e.,* a recombinant polypeptide comprising at least a fragment of the amino acid sequence of SEQ ID NO:3 or encoded by the nucleotide sequence of SEQ ID NO:2 -- required for the skilled artisan to correlate the function with a known structure.

As explained in the specification, the *H. pylori* cytotoxin causes formation of vacuoles in eukaryotic cells (Specification at page 5, lines 35-39 and page 46, lines 7-29, for example). The claimed recombinant polypeptide, however, exhibits substantially no toxicity, or substantially reduced toxicity. For example, the claimed polypeptide may be a genetically or chemically detoxified form of the cytotoxin, or a fragment of the native cytotoxin, having no toxicity. Additionally, the claimed polypeptide may exhibit substantially no toxicity or

substantially reduced toxicity by virtue of being recombinantly produced. Indeed, the recombinantly produced 95 kDa polypeptide taught by Manetti *et al.* (*Infection and Immunity*, 63(11):4476-4480 (1995)), though immunogenic, lacks toxicity. See also, Ghiara *et al.*, *Infection and Immunity*, 65(12) 4996-5002 (1997). Dr. Del Giudice has declared on the record that methods of chemical and genetic inactivation of toxins were known to those of skill in the art in March 1992. Moreover, Dr. Del Giudice has attested that it would have been routine to determine cytotoxin fragments that exhibit substantially no toxicity or substantially reduced toxicity. Toxicity could be measured, for example, in *in vitro* vacuolation assays and in animal models of *H. pylori* infection routinely used in the art.

Additionally, the specification discloses an example of a polypeptide that is immunologically identifiable by antibodies that react with the polypeptide of SEQ ID NO:3 (Specification at page 45, line 25 to page 46, line 6 (describing a fusion protein comprising the amino acids encoded by nucleotides 116-413 of SEQ ID NO:2 that generated rabbit antibodies that recognized the 100kDa *H. pylori* protein associated with vacuolation – *i.e.*, was immunologically identifiable by rabbit antibodies that recognize the toxic form of *H. pylori* cytotoxin)).

As the skilled artisan can envision the claimed polypeptide structure in accordance with the specification and would understand that the inventors were in possession of the claimed invention at the time of filing, claims 40, 54, 61-65, 72-75, 82-85, 93, and 94 satisfy the written description requirement of the first paragraph of section 112. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

IV. The claims are not anticipated by the Cover references.

Claims 40, 54, 61-65, 72-75, 82-86, 93, and 94 are rejected under 35 U.S.C. § 102 as allegedly being anticipated by U.S. Patent No. 6,054,132 to Cover *et al.* ("the '132 patent") or by Cover *et al.* (*J. Biol. Chem.*, 267:10570-10575 (1992)) ("the Cover article"). Applicants traverse the rejections.

Preliminarily, Applicants note that the Cover article is not prior art under 35 U.S.C. § 102(b).

To anticipate a claim, a prior art reference must teach, either expressly or inherently, each and every element of the claim. *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

The claims recite a recombinant polypeptide having at least a portion of the amino acid sequence of SEQ ID NO:3, or encoded by at least a fragment of the nucleotide sequence of SEQ ID NO:2, having the properties of being immunologically identifiable by antibodies that react specifically with the polypeptide of SEQ ID NO:3, or with the polypeptide encoded by SEQ ID NO:2, and exhibiting substantially no toxicity or substantially reduced toxicity.

In sharp contrast, the '132 patent discloses the purification from *H. pylori* broth culture supernatant of a vacuolating toxin having a molecular weight of 87 kDa wherein the purification scheme resulted in a greater than 5000-fold increase in specific activity of the toxin measured as a function of cell vacuolating activity ('132 patent, Table 1). In other words, the '132 patent does not teach, either expressly or inherently, a recombinant polypeptide of the present claims possessing substantially no toxicity or substantially reduced toxicity.

Similarly, the Cover article describes purification of the vacuolating toxin of *H. pylori* from broth culture supernatant resulting in a 5000-fold increase in specific activity, measured again as a function of cell vacuolation. Thus, the Cover article also does not teach, either expressly or inherently, a recombinant polypeptide of the present claims.

Applicants accordingly request reconsideration and withdrawal of the rejections.

Conclusion

Applicants submit that the present claims meet all the requirements for patentability. The Examiner is respectfully requested to allow all the present claims. If the Examiner is of a contrary view, she is invited to contact the undersigned attorney at (215) 557-5908.

Respectfully requested,

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